Natural Product Synthesis

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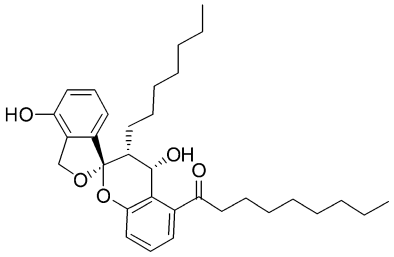
Total Synthesis of Paecilospirone**

*Tsz-Ying Yuen, Sung-Hyun Yang, and Margaret A. Brimble**

In 2000, Namikoshi et al. reported the isolation and structural elucidation of a novel [5,6]-bisbenzannulated spiroacetal[1] from the marine fungus *Paecilomyces* sp.[2] This unique spiro[chroman-2,1′(3′*H*)-isobenzofuran] derivative was identified as a potential antimitotic agent (20% inhibition at 50 μM) using an assay screening for microtubule assembly inhibitors and was subsequently named paecilospirone (**1**).[3]

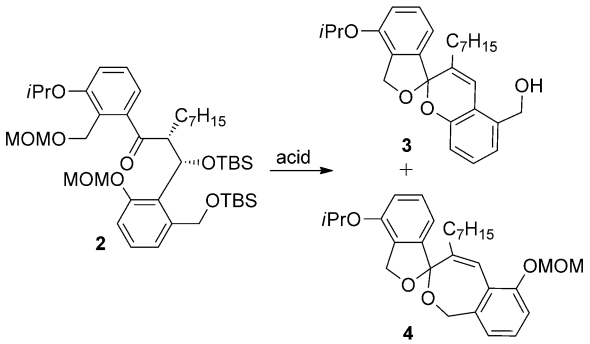


paecilospirone **1**

Despite the isolation of paecilospirone more than a decade ago, no total synthesis of this novel compound has yet been reported.[5] Herein, we present the first enantioselective synthesis of paecilospirone **1**.

Initial synthetic studies focused on the acid-catalyzed cyclization of ketone **2** to the spiroacetal core of paecilospirone (Scheme 1). However, under standard acidic conditions, ketone **2** readily underwent elimination to afford unsaturated spiroacetals **3** and **4**. This problem was exacerbated by the axial orientation of the hydroxy group positioned β to the spirocentre and *anti* to a vicinal hydrogen atom. Based on this observation, reaction conditions were carefully developed to assemble the spiroacetal core using a pH-neutral double deprotection/cyclization strategy.

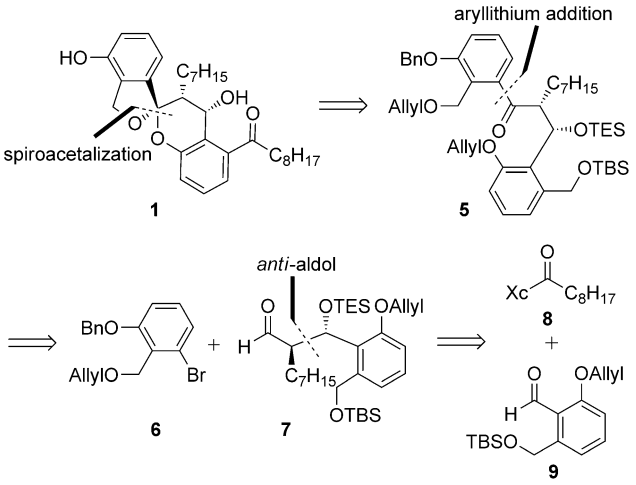
It was proposed that bis(allyl) ether ketone **5** would undergo palladium(0)-catalyzed removal of protecting groups and in situ spiroacetalization. In turn, ketone **5** would be constructed through addition of the aryllithium intermediate



Scheme 1. Standard acid-catalyzed deprotection/cyclization of ketone **2**, acid = $Bi(OTf)_3$, TMSBr, $NaHSO_4{\cdot}SiO_2$, CBr_4 or PPTS. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsiyl, PPTS = pyridinium *p*-toluenesulfonate.

derived from bromide **6** to aldehyde **7** (Scheme 2). An *anti*-selective aldol reaction between ketone **8** bearing a chiral auxiliary and aldehyde **9** should then establish the contiguous stereogenic centers in aldehyde **7**. Overall, the proposed retrosynthetic strategy was designed with maximum flexibility to allow production of a focused library of analogues for future biological evaluation.

Construction of aldehyde fragment **9** began with known aldehyde **10** (Scheme 3).[6] The phenolic moiety was protected as an allyl ether (**11**). Reduction of the aldehyde group and silyl protection of the resulting alcohol furnished **12**, which was subjected to a lithium–halogen exchange/formylation procedure to afford the requisite aldol precursor **9** in good overall yield (72%).



Scheme 2. Retrosynthetic analysis. Bn = benzyl.

[*] T.-Y. Yuen, S.-H. Yang, Prof. Dr. M. A. Brimble
Department of Chemistry
The University of Auckland
23 Symonds Street, Auckland (New Zealand)
E-mail: m.brimble@auckland.ac.nz
Homepage: http://web.chemistry.auckland.ac.nz/staffsites/brimbleM/

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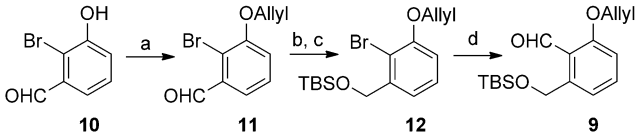
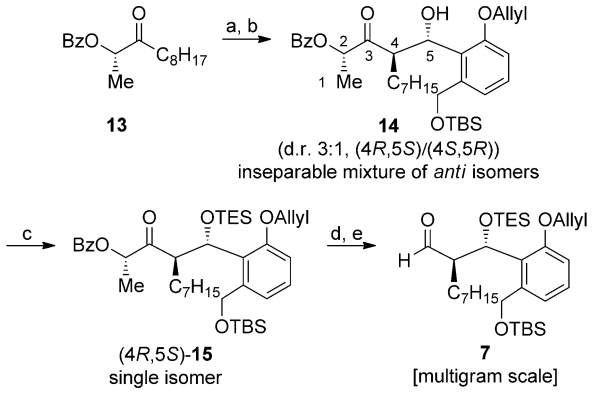


Scheme 3. Construction of aldehyde **9**. Reagents and conditions: a) K_2CO_3, allyl bromide, EtOH, reflux, 16 h, 93%; b) $NaBH_4$, EtOH, RT, 15 min; c) TBSCl, imidazole, DMF, RT, 16 h, 92% over two steps; d) *t*BuLi, Et_2O, −78 °C, 1 min; then DMF, −78 °C→RT, 14 h, 84%. DMF = *N*,*N*′-dimethylformamide.

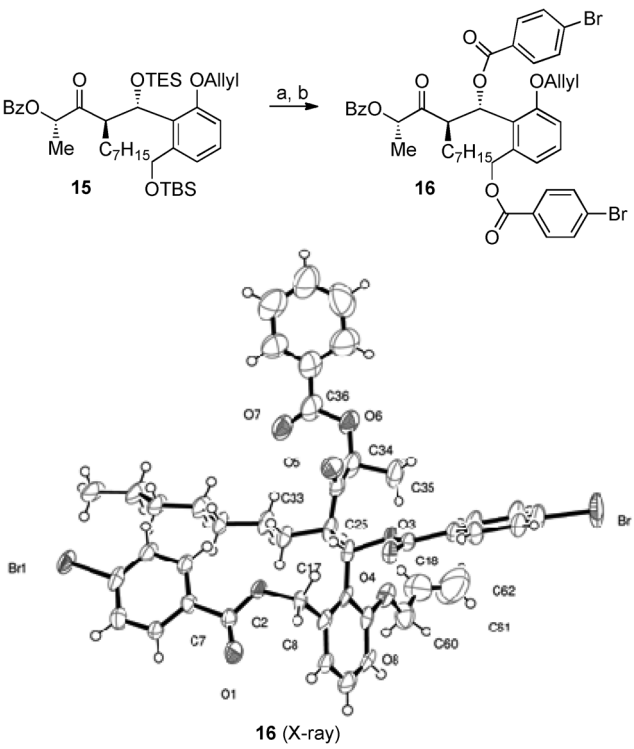
Initial attempts to access aldehyde **7** using Evans' $MgCl_2$-catalyzed *anti*-selective aldol methodology[7] only afforded the desired *anti*-aldol adduct in low yield (19%), albeit with high diastereoselectivity. Further modifications did not improve the yield to an acceptable level. The lack of success associated with the reaction was attributed to the highly sterically hindered nature of aldehyde **9**. Thus, an alternative aldol protocol based on the use of a lactate-derived CH(OBz)Me group as the chiral auxiliary was investigated.[8] Ketone **13** was synthesized using conditions similar to that described by Paterson et al. (Scheme 4).[8] Pleasingly, the



Scheme 4. Synthesis of aldehyde **7**. Reagents and conditions: a) *c*Hex_2BCl, Me_2NEt, Et_2O, 0 °C, 2 h; then **9**, −78 °C→−26 °C, 14 h; b) H_2O_2, pH 7 buffer, MeOH, 0 °C, 1 h, 79% over two steps (d.r. 3:1); c) TESOTf, 2,6-lutidine, CH_2Cl_2, −50 °C, 3 h, 65%; d) $LiBH_4$, THF, −78 °C→RT, 24 h; e) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 °C, 1 h, 50% over two steps. Bz = benzoyl, *c*Hex_2BCl = chlorodicyclohexylborane, TES = triethylsilyl, THF = tetrahydrofuran.

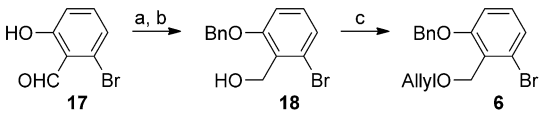
union of fragments **13** and **9** proceeded smoothly to afford an inseparable mixture of aldol diastereoisomers **14** in good yield (d.r. 3:1). Silyl protection of the β-hydroxy ketones **14** as TES ethers allowed separation of the individual *anti*-isomers.[9] Subsequent reductive cleavage ($LiBH_4$) of the benzoate ester and oxidative glycol cleavage with lead(IV) acetate[10] successfully delivered aldehyde **7** as the single 4*R*,5*S* isomer.

To establish the absolute configuration of the newly formed chiral centers, silyl ether **15** was treated with $Et_3N{\cdot}3HF$ and converted into bis(benzoate) derivative **16** (Scheme 5). The absolute configuration of **16** was unambiguously confirmed by single-crystal X-ray analysis.[11]



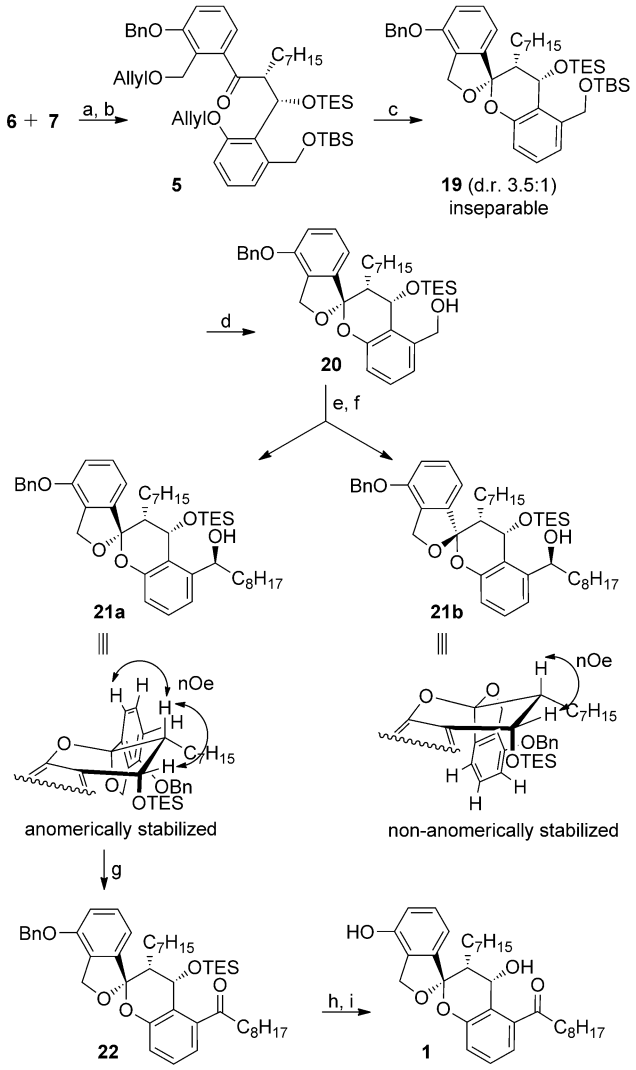
Scheme 5. Absolute configuration of bis(benzoate) **16**. a) $Et_3N{\cdot}3HF$, THF, 9 h; b) *p*-BrC_6H_4COCl, pyridine, 48 h, 60% over two steps.

Known benzaldehyde **17** (Scheme 6),[12] required for the preparation of bromide **6**, was readily synthesized from salicylaldehyde. Benzyl protection of the phenol group and subsequent reduction with $NaBH_4$ provided alcohol **18**, which underwent allylation to afford the required bromide coupling partner **6** (80% over 3 steps).



Scheme 6. Construction of bromide **6**. a) BnBr, K_2CO_3, TBAI, DMF, RT, 14 h, 99%; b) $NaBH_4$, EtOH, RT, 15 min, 90%; c) NaH, THF, 0 °C; then allyl bromide, TBAI, RT, 16 h, 90%. TBAI = tetrabutylammonium iodide.

Scheme 7 summarizes the final elaboration to paecilospirone **1**. Treatment of bromide **6** with *n*BuLi (1.3 equiv) and subsequent addition of aldehyde **7** at −78 °C afforded the corresponding alcohol as a diastereoisomeric mixture. Attempts to improve the yield of the addition using *t*BuLi were unsuccessful, rather, partial cleavage of the phenolic allyl ether took place.[13] Subsequent oxidation of the secondary alcohol yielded ketone **5**. Pleasingly, the critical double deallylation/spirocyclization was effected using catalytic Pd^0 in the presence of a PMHS–$ZnCl_2$ complex,[14] and provided advanced [5,6]-benzannulated spiroacetals **19** in 75% yield as an inseparable mixture of anomers (d.r. 3.5:1).



Scheme 7. Completion of paecilospirone **1**. Reagents and conditions: a) *n*BuLi, THF, −78 °C, 1 min; then **7**, −78 °C→RT, 14 h, 49%; b) DMP, pyridine, CH_2Cl_2, RT, 90 min, 93%; c) $[Pd(PPh_3)_4]$, PMHS, $ZnCl_2$, THF, RT, 24 h, 75% (ca. 3.5:1 mixture of anomers); d) $Et_3N{\cdot}3HF$, THF, 0 °C, 9 h, 77% after two cycles; e) TPAP, NMO, M.S. (4 Å), MeCN, 10 min, f) $C_8H_{17}MgBr$, THF, 0 °C→RT, 2 h, **21a** 60%, **21b** 13% over two steps after two cycles; g) TPAP, NMO, M.S. (4 Å), MeCN, 30 min, 85%; h) $Et_3N{\cdot}3HF$, THF, RT, 30 min, 88%; i) 10% Pd/C, H_2, MeOH, 6 h, 73%. DMP = Dess–Martin periodinane, M.S. = molecular sieves, NMO = 4-methylmorpholine *N*-oxide, nOe = nuclear Overhauser enhancement, PMHS = polymethylhydrosiloxane, TPAP = tetrapropylammonium perruthenate.

The primary TBS group was selectively removed in the presence of a secondary TES group using $Et_3N{\cdot}3HF$ under controlled conditions (0 °C, 9 h, unchanged starting material was recovered and recycled). TPAP oxidation[15] followed by immediate addition of octylmagnesium bromide to the crude aldehyde afforded readily separable alcohols **21a** and **21b** (as single isomers at the benzylic position) along with Grignard reduction product **20** (30%). The latter was recycled and all attempts to limit its formation using inorganic additives such as LiCl or $CeCl_3$[16] were unsuccessful.

The major isomer **21a** obtained from the spirocyclization step was confirmed to be anomerically stabilized by nOe experiments. Oxidation of benzyl alcohol **21a** and subsequent stepwise removal of the TES and benzyl groups furnished paecilospirone **1**. The spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS analyses) for the synthetic material were in full agreement with those reported for the natural product and the *ee* value was determined to be 95% by HPLC on a chiral stationary phase.[2,17]

In summary, the first total synthesis of paecilospirone **1** has been successfully executed in 19 steps in the longest linear sequence. Key features include the use of an *anti*-selective lactate-derived aldol reaction[8] between chiral ketone **13** and sterically congested aldehyde **9** and the novel application of a palladium(0)-catalyzed double deallylation/spirocyclization for the construction of the sensitive spiroacetal core. The overall approach is enantioselective, scalable, and highly amenable to the production of analogues. Synthesis and biological evaluation of such molecules may provide more potent antimitotic agents.

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